

**CHALLENGES AND OPPORTUNITIES IN CLINICAL
DRUG DEVELOPMENT**

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GOALS OF CLINICAL DRUG DEVELOPMENT LECTURE

CURRENT STATE ANALYSIS

TARGETED APPROACH TO DRUG DEVELOPMENT

**INFORMATION TO BE OBTAINED DURING
EACH DEVELOPMENT PHASE**

DECISION MAKING IN DRUG DEVELOPMENT

10-YEAR TRENDS IN MAJOR DRUG AND BIOLOGICAL SUBMISSIONS TO FDA

Line chart showing an overall decline in total submissions of NMEs and original BLAs to FDA for years 1993 through 2003. The greatest number of original BLAs received by FDA was approximately 70 in 1993 with a steep decline in numbers by 1994. The number of NMEs received by the FDA peaked in years 1996 and 1997 (approximately 44) and declined thereafter.

<http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html>

REASONS FOR DECLINE IN NDA SUBMISSIONS

↓ **“LOW HANGING FRUIT”**

↓ **MAJOR PHARMACEUTICAL COMPANIES**

↑ **REGULATORY BURDEN & COST**

INEFFICIENCIES IN DEVELOPMENT PROCESS

PHARMA SYNERGY: $N = 9 \rightarrow N = 1$

Flow chart showing successive mergers of major pharmaceutical companies.

DO MERGERS AFFECT THE RATE OF NEW DRUG DEVELOPMENT ?

POST-DISCOVERY PHASES OF DRUG DEVELOPMENT

Flow chart of the phases of drug development beginning with an IND and pre-clinical development through clinical development (Phase I – III) and then concluding in Phase IV (post marketing).

COMPOUND ATTRITION DURING DRUG DEVELOPMENT*

5	4.5-5	3.5	1.6	1.3	1
INDs Filed	Phase I	Phase II	Phase III	NDA Filed	NDA APR

*** Grudzinskas C. Portfolio & Project Planning & Management in
Atkinson AJ Jr, et al. Principles of Clinical Pharmacology**

SUCCESS RATES BY DRUG DEVELOPMENT PHASE*

Success rate (%) over year of entry into drug development phase from 1994 through 1998

<u>Phase I</u>	<u>Phase II</u>	<u>Phase 3</u>	<u>Pre-NDA</u>
75 to 63	45 to 30	88 to 48	180 to 85

Declining success rate apparent in all phases.

*** Wood AJJ. A Proposal for Radical Changes in the Drug Approval Process. N Engl J Med 2006; 355: 618-623.**

CLINICAL DEVELOPMENT COSTS*

CLINICAL PHASE	TIME (months)	<u>EXPECTED COSTS (\$ x 10⁶)</u>	
		OUT-OF-POCKET	CAPITALIZED**
PHASE I	12.3	15.2	30.5
PHASE II	26.0	16.7	29.5
PHASE III	33.8	27.1	37.4
TOTAL	72.1	59.0	97.4

* DiMasi JA, et al. J Health Econ 2003;22:151-85.

** BASED ON 11.9% COST OF CAPITAL

COSTS PER APPROVED DRUG*

	COST (\$ x 106)**	
	OUT-OF- POCKET	CAPITALIZED
TOTAL COSTS	403	802
CLINICAL COSTS	274	453
(% TOTAL)	(68%)	(56%)

*** DiMasi JA, et al. J Health Econ 2003;22:151-85.**

**** BASED ON 21.5% SUCCESS RATE**

**CLINICAL DEVELOPMENT PROGRAMS
OF SOME RECENTLY DEVELOPED DRUGS***

DRUG	FIH- NDA FILE	PHASE I	PHASE II	PHASE III	TOTAL
<u>INDICATION</u>	<u>(YEARS)</u>	<u>TRIALS/ SUBJECTS</u>	<u>TRIALS/ SUBJECTS</u>	<u>TRIALS/ SUBJECTS</u>	<u>TRIALS/ SUBJECTS</u>
HERCEPTIN® BREAST CA	6 - 10	3/48	8/532	1/469	12/1069
ENBREL® RHEUM. ARTHRITIS	6 - 7	8/163	23/503	23/1381	34/2048
RELENZA® INFLUENZA	4 - 5	18/446	3/3275	3/1588	28/5309
VIAGRA® ERECT. DYSFUNCT.	5	42/905	13/498	13/4679	68/6082
VIOXX® OA & PAIN	4 - 5	31/940	2/1855	13/5733	46/8528

* Grudzinskas C. Design of clinical development programs in
Atkinson AJ Jr, et al. Principles of Clinical Pharmacology

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**WHAT DOES THIS
EXPENDITURE PRODUCE?***

**“We Sell Only the Package Insert,
We Give Away the Product !”**

* Grudzinskas C. Design of clinical development programs in
Atkinson AJ Jr, et al. Principles of Clinical Pharmacology

CENTRAL ROLE OF DRUG LABEL

THE DRUG LABEL IS THE PRIMARY SOURCE OF DRUG PRESCRIBING INFORMATION AND IS REVIEWED BY THE FDA AS PART OF THE DRUG APPROVAL PROCESS.

AS SUCH, THE DRUG LABEL IS A DISTILLATE OF THE ENTIRE DRUG DEVELOPMENT PROCESS.

DESPITE THIS, THE DRUG LABEL OFTEN IS CREATED AS AN AFTERTHOUGHT.

INFORMATION CONTENT OF CURRENT DRUG LABELS*

CORE INFORMATION CATEGORY	INCLUSION OF DESIRABLE DATA ELEMENTS MEAN (95% CI)
MECHANISM OF ACTION	88% (84% - 93%)
PHARMACODYNAMICS	43% (37% - 49%)
DRUG METABOLISM	23% (16% - 29%)
PHARMACOKINETICS	42% (35% - 49%)
DOSE ADJUSTMENT	37% (32% - 42%)

* Spyker DA, et al. Clin Pharmacol Ther 2000;67:196-200.

PATHOPHYSIOLOGIC FACTORS NOT ACCOUNTED FOR IN DRUG DOSING*

A pie chart is shown that indicates the following factors not accounted for in drug dosing:

Advanced age 42%
Renal impairment 33%
Patient weight 19%
Other 6%

* Lesar TS, Briceland L, Stein DS. JAMA 1997;277:312-7.

TARGETED APPROACH TO DRUG DEVELOPMENT*

Whenever a decision is made to develop a compound, two fundamental components of the development plan should be the Target Product Profile (TPP) and the Target Package Insert (TPI).

TPP: Specific targets for compound, including toxicology, pharmaceutical development, manufacturing, clinical research, clinical safety, etc. (~ 40 - 80 pages)

TPI: Draft label for compound that is amended as data accumulate (~ 3 – 10 pages)

*** Tansey, M. Targeted treatment solutions. 11th EUFEPS Conference on Optimising Drug Development. Basel, December 8-10, 2003.**

TARGET PRODUCT PROFILE (TPP) *

A document in which “the sponsor specifies the labeling concepts that are the goals of the drug development program, documents the specific studies intended to support the labeling concepts, and then uses the TPP to assist in a constructive dialogue with the FDA.”

*** CDER Draft Guidance: <http://www.fda.gov/cder/guidance/6910dft.pdf>**

FDA GOALS OF TARGETED PRODUCT DEVELOPMENT *

**TO HELP SPONSORS DESIGN, CONDUCT, AND
ANALYZE CLINICAL TRIALS TO OPTIMIZE
PURSUIT OF THE DESIRED OUTCOME**

**TO PROMOTE A SHARED UNDERSTANDING
OF A SPONSOR'S DRUG DEVELOPMENT
PROGRAM**

**TO PROVIDE A FORMAT FOR DISCUSSIONS
BETWEEN SPONSORS AND THE FDA**

*** CDER Draft Guidance: <http://www.fda.gov/cder/guidance/6910dft.pdf>**

UTILITY OF TPP FOR SPONSOR

**PROVIDES FOCUS FOR PLANNING
CLINICAL TRIALS**

**SERVES AS A CONTRACT BETWEEN
DEVELOPMENT AND MARKETING**

**PROVIDES BASIS FOR CORPORATE
DECISION MAKING**

**THEREFORE, OF MAXIMAL BENEFIT
IF DRAFTED EARLY IN THE DRUG
DEVELOPMENT PROGRAM**

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PHASE I GOALS

DOSE PROPORTIONALITY

ELIMINATION-PHASE $T_{1/2}$

ADEQUATE BA FOR ORAL ADMINISTRATION

METABOLIC PATHWAYS

EVIDENCE OF PHARMACOLOGIC ACTIVITY

NONCANCER DRUGS CAUSING ADR'S*

PHENYTOIN

PREDNISONE

DIGOXIN

AMIODARONE

ASPIRIN

CO-TRIMOXAZOLE

PENTAMIDINE

CARBAMAZEPINE

CODEINE

LITHIUM

THEOPHYLLINE

DESIPRAMINE

DEXAMETHASONE

GENTAMICIN

* 1988 NMH DATA (CLIN PHARMACOL THER 1996;60:363-7)

LEVELS NOT PROPORTIONAL TO DOSE

Nonlinear kinetics.

Plot showing phenytoin ($\mu\text{g/mL}$) from 0 to 50 over phenytoin dose (mg/day) from 0 to 300.

STEADY STATE EQUATIONS

FIRST ORDER KINETICS

$$\text{DOSE}/\tau = \text{CL}_E \times \bar{C}_{SS}$$

MICHAELIS – MENTEN KINETICS

$$\text{DOSE}/\tau = \frac{[V_{MAX}]}{[K_m + C_{SS}]} \bar{C}_{SS}$$

DOSE DEPENDENCY ?

AUC = AREA UNDER PLASMA LEVEL VS. TIME CURVE

Increase: Dose = 4-Fold

AUC = 13.6-Fold

100 mg Dose

AUC = 17.91 $\mu\text{g}\cdot\text{hr}/\text{ml}$

25 mg Dose

AUC = 1.32 $\mu\text{g}/\text{hr}/\text{ml}$

PSEUDO DOSE DEPENDENCY

Plot showing [DRUG] ($\mu\text{g/ml}$) from 0.5 to 10.0 over hours (0 through 7) indicating the limit of assay sensitivity at 0.7

Increase: Dose = 4-Fold	AUC = 13.6-Fold
100 mg Dose	AUC = 17.91 $\mu\text{g}\cdot\text{hr/ml}$
25 mg Dose	AUC = 1.32 $\mu\text{g}\cdot\text{hr/ml}$

CLOTTING FACTOR PHARMACOKINETICS*

“THE V(dss)..... ALWAYS EXCEEDS THE ACTUAL PLASMA VOLUME, IMPLYING THAT NO DRUG, NOT EVEN LARGE MOLECULAR COMPLEXES AS FVIII, IS ENTIRELY CONFINED TO THE PLASMA SPACE.”

“A TOO SHORT BLOOD SAMPLING PROTOCOL GIVES FLAWED RESULTS NOT ONLY FOR TERMINAL T $\frac{1}{2}$ BUT ALSO FOR THE MODEL INDEPENDENT PARAMETERS.”

*** Berntorp E, Björkman S. Haemophilia 2003;9:353-9.**

DISTRIBUTION VOLUME OF REPRESENTATIVE MACROMOLECULES

MACROMOLECULE	MW (kDa)	V ₁ (mL/kg)	V _{d(ss)} (mL/kg)
INULIN	5.2	55 IVS	164 ECF
FACTOR IX (FIX)	57	136	271
INTERLEUKIN-2 (IL-2)	15.5	60	112
INTERLEUKIN-12 (IL-12)	53	52	59
GRANULOCYTE COLONY STIMULATING FACTOR (G-CSF)	20	44	60
RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR (RT-PA)	65	59	106

PHASE II GOALS

PROOF OF CONCEPT

THERAPEUTIC EFFICACY

SATISFACTORY EARLY SAFETY DATA

DOSE RESPONSE

BIOMARKER

CLINICAL ENDPOINT

FREQUENCY OF DOSE ADMINISTRATION

SIMVASTATIN DOSE-RESPONSE STUDY*

NUMBER OF 1° ↑ CHOL PATIENTS:	43
NUMBER OF STUDY CENTERS	4
STUDY DURATION:	6 weeks
SIMVASTATIN DOSE RANGE:	
ONCE DAILY:	2.5 - 40 mg/day
TWICE DAILY:	1.25 - 40 mg bid

* Mol MJTM et al. Lancet 1986;ii:936-9

ESTIMATING DOSE RANGE FOR SUBSEQUENT PIVOTAL TRIAL

Line chart showing % of cholesterol decrease, from 0.0 to 40.0, with increased dose (from 0 to 80 mg/day) of simvastatin. The MDSE is 20 mg/day.

Mol MJTM, et al. Lancet 1986;ii:936-9.

POST-MARKETING DRUG DOSE CHANGES BASED ON PDR REVIEW*

DRUGS EVALUATED (354)

DOSE CHANGES (73 = 21% EVALUATED DRUGS)

DOSE INCREASES (15 = 21% OF CHANGES)

DOSE DECREASES (58 = 79% OF CHANGES)

↓ **DOSE STRENGTH**

↓ **TREATMENT DURATION**

↑ **DOSE INTERVAL**

POPULATION RESTRICTION

REMOVAL OF INDICATION

* Cross J, et al. *Pharmacoepidemiol Drug Safe* 2002;11:439-46.

DOSE DISCREPANCIES BETWEEN PDR & MEDICAL LITERATURE*

DRUG **	PDR INITIAL DOSE (mg)	EFFECTIVE LOWER DOSE (mg)
ACEBUTOLOL	400	200
CELECOXIB	100 BID	50 BID
LISINOPRIL	10	5
OMEPRAZOLE	20	10
PROPRANOLOL	80	40

* Cohen JS. Arch Intern Med 2001;161:957-64.

** SELECTED FROM A TABLE OF 48 COMMONLY PRESCRIBED DRUGS

PHASE III GOALS

PIVOTAL TRIALS

CONFIRM EFFICACY

EVALUATE SAFETY

POPULATION PK OR SPECIAL STUDIES

EFFECTS OF ORGAN DYSFUNCTION

DRUG INTERACTIONS

COMPARE WITH STANDARD THERAPY

EVALUATE BIOMARKER VS. CLINICAL ENDPOINT

SIMVASTATIN SURVIVAL STUDY*

NUMBER OF CHD PATIENTS: 4444

NUMBER OF STUDY CENTERS: 94

MEDIAN FOLLOW-UP DURATION: 5.4 years

SIMVASTATIN DOSING:

INITIAL: 20 mg/day

SUBSEQUENT TITRATION: ↓[Chol] to 117-200 mg/DL

*** 4S Study Group. Lancet 1994;344:1383-9**

KAPLAN-MEIER CURVES FOR ALL-CAUSE MORTALITY*

Line chart showing proportion of patients on Simvastatin and placebo still alive by years (0 through 6) since randomization. Simvastatin treatment increases survival.

RR = 0.70 (0.58-0.85)

Log-rank p=0.0003

*** Scandinavian Simvastatin Survival Study Group. Lancet 1994;344:1383-9.**

PHASE IV GOALS

NEW INDICATIONS

ACTIVE COMPARATOR TRIALS

NEW PATIENT GROUPS

PEDIATRICS (See FDA Guidance*)

PREGNANT WOMEN (See FDA Guidance*)

PHARMACOVIGILANCE

* <http://www.fda.gov/cder/guidance/index.htm>

PHASE IV STUDY: ARA-C “USELESS” *

SPONSOR: AIDS CLINICAL TRIALS GROUP

**GOAL: EVALUATE EFFICACY OF INTRATHECAL (IT)
CYTARABINE (ARA-C) IN PATIENTS WITH PROGRESSIVE MFL**

*** Hall CD, et al. N Engl J Med 1998;338:1345-51.**

MULTIFOCAL LEUKOENCEPHALOPATHY (MFL)

OCCURS IN 4% OF PATIENTS WITH AIDS

THERE IS NO ESTABLISHED EFFECTIVE THERAPY

SURVIVAL AVERAGES 2.5 TO 4 MONTHS

OCCURRED IN PATIENTS RX'D WITH TYSABRI

OCCURRED IN PATIENTS RX'D WITH RITUXAN

LABELLED INDICATIONS FOR CYTARABINE (ARA-C)

IV for remission induction of acute non-lymphocytic leukemia (in combination with other approved cancer drugs).

IV for treatment of acute lymphocytic leukemia

IV for treatment of blast phase of chronic myelocytic leukemia.

IT for prophylaxis and treatment of meningeal leukemia.

RATIONALE FOR PHASE IV STUDY

The JC virus (etiologic agent of progressive multifocal leukoencephalopathy) is sensitive to ARA-C *in vitro*.

ARA-C crosses the blood-brain barrier (BBB) only slowly.

Intrathecal/intraventricular administration might improve the therapeutic efficacy of ARA-C by circumventing the BBB.

PATIENT ENROLLMENT

**57 PATIENTS WITH PML RANDOMIZED IN
MULTICENTER ACTG TRIAL**

THREE TREATMENT GROUPS

**ONLY CONTINUE ANTIRETROVIRAL DRUGS
ADD 4 MG/KG ARA-C DAILY IV FOR 5 d q 21 d
ADD INTRATHECAL ARA-C**

IT DOSE REGIMEN: 19 SUBJECTS

“GROUP 3 RECEIVED ANTIRETROVIRAL THERAPY PLUS 50 MG OF CYTARABINE, ADMINISTERED INTRATHECALLY WITH AN OMMAYA RESERVOIR, ONCE A WEEK FOR FOUR WEEKS, THEN ONCE EVERY 2 WEEKS FOR 8 WEEKS, THEN ONCE EVERY 4 WEEKS FOR THE REMAINDER OF THE STUDY.”

REPETITIVE IT ADMINISTRATION IS NON-TRIVIAL

Photograph of an ommaya pump

SCHEMATIC OF PUMP PLACEMENT

Graphic illustration of a lateral view of brain with an Ommaya pump inserted in the frontal lobe of the brain.

RESERVOIR PLACEMENT

Photograph of the side view of the upper half of a man's head with an arrow indicating where the reservoir should be placed (upper back of head).

ELEMENTS OF STUDY DESIGN

STATISTICAL SAFEGUARDS

**RANDOMIZATION OF PATIENTS
BALANCED TREATMENT GROUPS
INTENTION TO TREAT ANALYSIS
DATA ANALYZERS BLINDED**

**JUSTIFICATION FOR IT DOSE REGIMEN
NONE PROVIDED**

THE MOST WIDELY USED BIOMARKER/SURROGATE ENDPOINT

DRUG LEVELS USED AS A SURROGATE FOR CLINICAL EFFICACY AND
TOXICITY IN THE EVALUATION OF GENERIC DRUGS *

IN VITRO ESTIMATES OF EFFECTIVE DRUG LEVELS WIDELY USED
AS A BIOMARKER IN DEVELOPING ANTI-INFECTIVE DRUGS

* **Comment by Carl Peck: CDDS WORKSHOP, McLean,
VA, May 13, 1998**

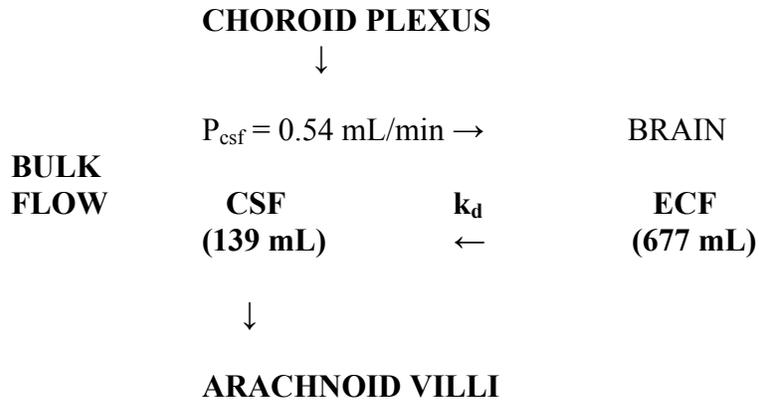
INTRATHECAL AMPHOTERICIN B PHARMACOKINETICS

Two plots of amphotericin concentration (mcg/mlCSF) hours, from 0 to 26, after intrathecal injection. One plot shows amphotericin concentration levels in patients after the administration of 100 mcg on 12/17/66. The other plot shows amphotericin levels in patients after the administration of 300 mcg on 12/27/66.

MIC *C. neoformans*

From: Atkinson AJ Jr, Bindschadler DD: Am Rev Resp Dis 1969;99:917-24.

MODEL FOR ANALYZING INTRATHECAL AMPHOTERICIN B PHARMACOKINETICS



From: Atkinson AJ Jr, Bindschadler DD: Am Rev Resp Dis 1969;99:917-24.

INTRATHECAL CYTARABINE PHARMACOKINETICS

Plot showing μM (from 1.0 to 1000) over time (0 to 24 hours) for ARA C (ventricular), ARA U (ventricular), and ARA C (lumbar).

CLE = 0.42 mL/min

↑ 30 mg ARA-C, IT

**From: Zimm S, Collins JM, Miser J, Chatterji D, Poplack DG:
Clin Pharmacol Ther 1984;35:826-30.**

SIMULATED CYTARABINE INTRATHECAL DOSE REGIMENS

Line charts showing Ara-C CSF Concentration (from 0.1 to 1mM) over time from 0 to 3 days following administration of 30 mg qd x 3 and 70 mg.

The minimum cytotoxic level is also shown at 1 μ M as the in vitro effective level for JC virus.

**From: Zimm S, Collins JM, Miser J, Chatterji D, Poplack DG:
Clin Pharmacol Ther 1984;35:826-30.**

**“FAILURE” OF IT CYTARABINE IN PML ASSOCIATED
WITH HIV INFECTION***

Copy of the title and authors of the journal article entitled, “Failure of Cytarabine in progressive multifocal leukoencephalopathy associated with HIV infection” by Colin D. Hall, M.B., CH.B., et al

**SINCE THE CHOSEN IT DOSE HAD NO POSSIBILITY OF BEING
EFFECTIVE, IT IS ERRONEOUS TO CONCLUDE THAT THE DRUG IS
INEFFECTIVE.**

*** Hall CD, et al. N Engl J Med 1998;338:1345-51.**

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PHASE**

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GO – NO GO DECISIONS

WHY DRUG DEVELOPMENT FAILS

UNSUITABLE BIOPHARMACEUTICAL PROPERTIES

UNSUITABLE CLINICAL PK

PHARMACOLOGY DOESN'T WORK IN HUMANS

UNEXPECTED TOXICITY IS ENCOUNTERED

* Ronald E. White, Bristol-Myers Squibb (From Good Ligands to Good Drugs, AAPS-NIGMS Symposium, February 19-21, 1998)

GO – NO GO DECISIONS

**COMPOUND RICH ENVIRONMENT
COMBINATORIAL CHEMISTRY
HIGH THROUGHPUT SCREENING**

**FAIL EARLY PARADIGM DRIVEN BY CLINICAL DEVELOPMENT
COSTS**

COMPOUND ATTRITION DURING DRUG DEVELOPMENT*

5	4.5-5	3.5	1.6	1.3	1
INDs Filed	Phase I	Phase II	Phase III	NDA Filed	NDA APR

*** Grudzinskas C. Portfolio & Project Planning & Management in
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IDEAL DISTRIBUTION OF COMPOUND ATTRITION*

Bar chart showing this distribution from 0% to 60% for Pre-FIH (approximately 60%), Ph.1 (approximately 30%), Ph.2 (approximately 2%), Ph.3 (approximately 1%), and NDA (also about 1%).

*** Grudzinskas C. Principles of Clinical Pharmacology Course 2002.**

DECISION MAKING IN DRUG DEVELOPMENT

GO – NO GO DECISIONS

LESSER IMPACT DECISIONS

THREE MOST IMPORTANT CONSIDERATIONS IN MARKETING *

DIFFERENTIATION

DIFFERENTIATION

DIFFERENTIATION

Photograph of *Roberto C. Goizueta – 1931-1997 (former CEO Coca Cola) holding a bottle of Coca Cola.

SENSITIVITY ANALYSIS FOR A HYPOTHETICAL ANTIBIOTIC

	NPV	\$0.3B	\$1B	\$3B
NDA Filing	18 MOS	_____	12 months	_____ 6mos.
Doses per day	TID	_____	BID	_____ QD
Concomitant use	None	_____		All
Sensitivity test available	No	_____		Yes
COGs	\$70k/kg	_____		\$10k/kg
Availability of IV at launch	No	___		Yes

*** Grudzinskas C. Portfolio & Project Planning & Management
in Atkinson AJ Jr, et al. Principles of Clinical Pharmacology**

PHARMACEUTICAL PRODUCT LIFE CYCLE

Lead identification

Lead optimization

Pre-clinical development

Clinical development

Regulatory review

Scale up & launch

Post marketing

Patent expiration

*** Adapted from *Pharmaceutical Executive*, January 2000, page 80**

PROLONGING PRODUCT LIFE CYCLE

POST-MARKETING STRATEGIES
DEVELOP NEW INDICATIONS
OBTAIN PEDIATRIC LABEL

PATENT EXPIRATION STRATEGY
Rx TO OTC SWITCH
FRANCHISE GENERIC

MANAGEMENT CONSIDERATIONS

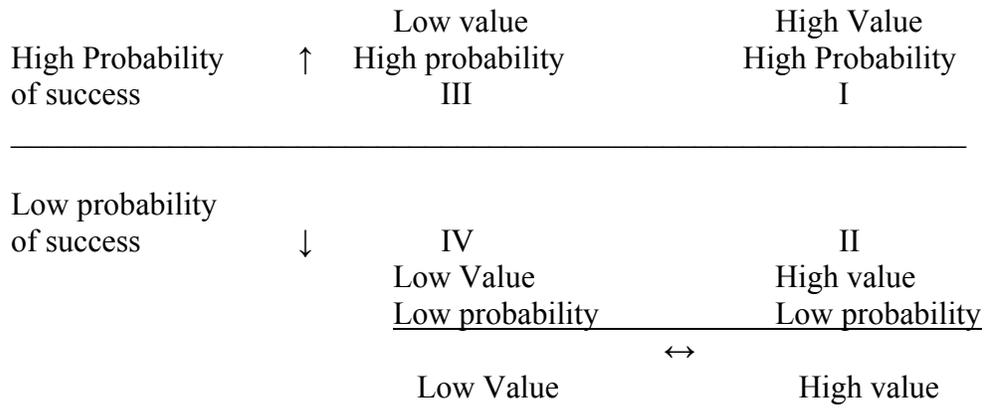
PORTFOLIO DESIGN

MATRIX STRUCTURE

TIME-RESOURCE TRADE OFFS

STRATEGIES AND CHALLENGES

PORTFOLIO ANALYSIS



* Grudzinskas C. Portfolio & Project Planning & Management
 in Atkinson AJ Jr, et al. Principles of Clinical Pharmacology

MANAGEMENT CONSIDERATIONS

Photograph of the sun setting in an apparently rural area with a barn and four silos. On each silos, going from left to right, one word is indicated on it. The words, and order that they are in, from left to right, follow below:

Discovery

Pre-clinical

Clinical

Marketing

MATRIX MANAGEMENT STRUCTURE

Project Teams

DISCIPLINE	<u>LINE MANAGEMENT</u>								
	Discovery	Toxi-cology	PK	BIO-STAT.	DATA MGMT.	MEDICAL	REG-ULATORY	PRO-JECT MGMT.	MAR-KETING
PROJECT 1	X	X	X			X	X	X	X
PROJECT 2	X	X	X	X	X	X	X	X	X
PROJECT 3	X	X	X	X	X	X	X	X	X
PROJECT N			X	X	X	X	X	X	X

PROJECT TEAM CONSIDERATIONS

STAFF QUALITY & CONTINUING EDUCATION

LEVEL OF PROJECT TEAM AUTONOMY

INCENTIVIZE EARLY NO-GO DECISIONS

CO-LOCALIZATION OF TEAMS

RESOURCE ALLOCATION

HEAVYWEIGHT PROJECT TEAMS

BUDGET

EQUIPMENT

THE PROJECT MANAGEMENT TRIANGLE

Time (Schedules, deadlines)

Resources (people, equipment, \$\$\$)



Specifications
(Quality and quantity)

*** Grudzinskas C. Portfolio & Project Planning & Management
in Atkinson AJ Jr, et al. Principles of Clinical Pharmacology**

Servant Leadership

Photograph of a book cover entitled, Leadership is an Art by Max DePree including the following book review:

“This book is thoughtful, personal, human, persuasive. Give it to a daughter, son, or Fortune 500 Chairman. They should bless you for years to come.” – Tom Peters